REMARKS

With entry of the current amendment, claims 1, 5-7 13, 15, 18, and 30 have been amended and claims 16, 17, 25-29 and 48-61 have been cancelled. Claims 4, 8-12, 14, 19-24, 32-47, and 62-67 were previously cancelled; accordingly, claims 1-3, 5-7, 13, 15, 18, 30, and 31 are pending in the application. Applicants respectfully request cancellation of the claims without prejudice to revival for subsequent prosecution.

Although the Office Action acknowledges in paragraph 2 that claim 14 was previously cancelled, Applicants respectfully note that claim 14 was indicated as pending on the Office Action Summary.

The amendments to the claims add no new matter and are supported throughout the application as filed.

Claims 1, 13, and 18 have been amended to recite a nucleic acid that encodes a polypeptide that transduces an increase in intracellular calcium. Support can be found, *e.g.*, in the specification at page 10, lines 4-10.

Claim 3 has been amended to recite a nucleic acid encoding a polypeptide comprising at least 200 contiguous amino acids of SEQ ID NO:2. Support can be found, *e.g.*, in the specification at page 18, lines 8-10 and lines 29-30. These passages indicate that two or more polypeptide sequences can be the same over a specified region (lines 8-10) and that a region can be 200 contiguous positions of a sequence (lines 29-30).

Claims 5 and 18 recite hybridization conditions comprising 50% formamide, 5 X SSC, and 1% SDS; and wash conditions comprising 0.2X SSC and 0.1% SDS at 65°. Support can be found, *e.g.*, on page 21, lines 11-13.

Claim 15 recites a nucleic acid encoding a polypeptide comprising at least 95% identity to the amino acid sequence of SEQ ID NO:2. Support can be found, *e.g.*, on page 11, lines 11-16 and page 18, lines 8-10.

For convenience, the objections/rejections are addressed in the order presented in the Office Action.

Objections to the specification

The specification was objected to because it contains an embedded hyperlink and an informality related to the use of acronyms.

The amendment to the specification at the paragraph on page 19 removes the hyperlink. The amendment to the paragraph on page 5, indicates that EDG stands for "endothelial differentiation gene". The term "TGR" is not used as an acronym, rather it is an internal designation used by Applicants.

Rejection under 35 U. S. C. § 101, utility

Claim 1-3, 5-7, 13, 15-18, 30, and 31 were rejected as allegedly lacking utility. The Examiner contends that the claimed invention lacks a well-established, or a specific, substantial and credible utility. In paragraph 8, the Examiner notes that evidence supporting the assertion that SEQ ID NO:1 encodes a polypeptide having a specific function similar to a known G-protein coupled receptor would be viewed favorably as evidence of patentable utility. Although Applicants disagree with the Examiner assertions, in order to expedite prosecution, a Declaration under 37 C.F.R. § 1.132 by Daniel Lin is provided to supply the additional evidence.

The Declaration presents data showing that murine TGR18, which is encoded by SEQ ID NO:1, has a known G-protein coupled receptor activity, *i.e.*, it transduces an increase in intracellular calcium. As Dr. Lin explains, GPCR activity can be assessed using a variety of common assays. One such assay is an Aequorin assay. Aequorin assays are widely used in the art to measure GPCR-mediated increases in intracellular calcium. The assay involves the use of the Ca^{2+}-sensitive photoprotein aequorin. The aequorin complex contains the apo-aequorin protein, molecular oxygen, and the luminophore coelenterazine. The binding of calcium ions disrupts the complex, leading to the emission of blue light, which provides a means of determining increases in intracellular calcium.

As set forth in the Declaration, mouse, human, and rat TGR18 GPCR activities were tested in an Aequorin assay. Briefly, CHO cells were transiently co-transfected with 10 μg of an Aequorin reporter gene and 10 μg of a cDNA encoding human TGR18, mouse TGR18, rat TGR18, or a vector control. The mouse TGR18 expression vector comprises the coding region

of the cDNA sequence presented in SEQ ID NO:1, which encodes the protein of SEQ ID NO:2. Following transfection, the cells were harvested and re-suspended in buffer containing coelenterazine f. Aequorin luminescence was determined following incubation of the harvested cells with ligand. The results, shown in Figure 1, demonstrate that mouse, human, and rat TGR18 all have GPCR activity: they each transduce an increase in intracellular calcium.

The specification teaches that GPCR activity can be assessed using a variety of assays to determine functional effects. These include changes in calcium ion levels (*see, e.g.*, page 11, lines 8-10 and page 39, lines 27-30). The exemplary data provided in the Declaration thus provide additional evidence that TGR18 has a well-known GPCR activity, which is asserted in the specification.

In view of the above, Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, enablement

Claims 1-3, 5-7, 13, 15-18, 20, and 31 were also rejected as allegedly not enabled because one of skill in the art would not know how to use the invention due to the alleged lack of utility. Applicants traverse for the reasons set forth in the previous section.

In addition, the claims that relate to variants and fragments of SEQ ID NO:2 were rejected as not enabled. The rejection alleges that the specification lacks adequate guidance regarding the structural features that are required for activity and that it would require undue experimentation to make and use the claimed nucleic acid sequences. In particular, the Examiner argues that it would require undue experimentation to identify the claimed sequences because of unpredictability in predicting structure/function relationships. Applicants respectfully traverse.

As the Examiner knows, it is well settled in the biotechnology art that routine screening of even large numbers of samples is not undue experimentation when a probability of success exists. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As stated in *Wands*, "enablement is not precluded by the necessity for some experimentation, such as routine screening." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, as set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments." The application provides guidance to make the claimed sequences

based on structural properties and guidance for performing assays to assess the function of the sequences. Thus, although such analyses could conceivably require analyzing a large number of sequences, the practitioner could reasonably expect to be able to successfully identify sequences that fall within the scope of the invention.

In the present case, the claims are drawn to isolated nucleic acids that encode a polypeptide that has a G protein coupled receptor activity, *i.e.*, the ability to transduce an increase in intracellular calcium, and structural features set forth in the claims, *i.e.*, reference nucleic acid or amino acid sequences. The application teaches reference nucleic acid and polypeptide sequences (SEQ ID NOs: 1 and 2, respectively), and describes the known structural features of GPCRs (*see, e.g.*, page 10, lines 20-27). The practitioner is also directed to routine techniques for making such sequences (*see, e.g.*, the section starting on page 24 of the application), and commonly used methods to assess GPCR activity, including methods of determining changes in intracellular calcium ion levels (*see, e.g.*, page 41, line 30, bridging to page 42, line 8 and page 43, lines 3-10). Thus, the disclosure in the specification, along with methodology well known to those of skill in the art, provide ample direction for screening nucleic acids encoding GPCRs having the claimed structural and functional characteristics.

Regarding the issue of enablement of nucleic acids where a large number of possible embodiments exist, the PTO has provided express guidelines for examination. As noted above, a rejection for undue breadth is inappropriate where one of skill could readily determine any one of the claimed embodiments (MPEP § 2168.08). In the present application, one of skill needs to identify nucleic acids that have a high level of identity with respected to a conserved reference sequence or have a particular number of contiguous amino acids with reference to a conserved reference and hybridize under specific conditions to the conserved reference nucleotide sequences. Although many such nucleic acids are possible, one of skill can readily determine, one by one, any particular sequence that has these properties without undue experimentation.

In light of the above arguments, Applicants respectfully submit that all of the claims pending with entry of this Amendment are fully enabled, and request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, written description

Claims 1-3, 5-7, 13, 15-18, 30, and 31 were rejected as allegedly lacking adequate written description support. The Examiner contends that the specification does not describe variants and fragments of the claimed GPCRs and that the claims therefore are not properly described. Applicants respectfully traverse.

The Federal Circuit has held that the written description requirement can be fulfilled in any number of ways, so long as the specification describes the invention "in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention." See, *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997). For a chemical invention, an adequate description "requires a precise definition, such as by structure, formula, chemical name, or physical properties...."

In the present case, the claims are directed to compositions and methods encompassing a nucleic acid encoding a protein at least 90% identical to SEQ ID NO:2 or a protein comprising a contiguous segment of SEQ ID NO:2. The proteins also have a function: they transduce an increase in intracellular calcium. Thus, the claim language defines physical and structural properties of the invention, as explicitly required by the court in *University of California*.

Further, the examples in The Revised Written Description Examination Guidelines, Federal Register, Vol. 66, No.4, 1099, Jan. 5, 2001, directly relate to the present application. In Example 14 of the Guidelines, variants of a protein that have at least 95% identity to a sequence and catalyze a reaction, *i.e.*, they have a function, are claimed. Example 14 describes, but does not exemplify, variants of the protein, including substitutions, deletions, and insertions, and indicates that procedures for making the protein are routine in the art. The specification also describes an assay for detecting protein activity. The analysis indicates that the single disclosed species is representative of the claimed genus because all members must have the particular structural feature, at least 95% identity to the reference compound, and functional feature. The Conclusion of Example 14 states that the disclosure meets the

requirements of 35 U.S.C. § 112 as providing adequate written description for the claimed invention.

In another example from the Guidelines, Example 9, nucleic acid sequences that specifically hybridize under highly stringent conditions to a reference sequence are claimed. Example 9 discloses a single species, an activity of the protein, and provides examples of stringent hybridization conditions. The Conclusion states that the claim is adequately described.

The present claims relate to nucleic acids that encode proteins that have both specific structural and functional features. Thus, in view of the Guidelines, the present claims are adequately described.

For the reasons explained above, Applicants respectfully submit that the specification meets the description requirement and, accordingly, request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 18 was rejected as allegedly indefinite in the recitation of the term "stringency". The claims have been amended to recite specific hybridization and wash conditions. Applicants therefore believe that the rejection has been obviated and request its withdrawal.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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